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Review article

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Contemporary pharmacological treatment and management of heart failure

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Abstract

The prevention and treatment strategies for heart failure (HF) have evolved in the past two decades. The stages of HF have been redefined, with recognition of the pre-HF state, which encompasses asymptomatic patients who have developed either structural or functional cardiac abnormalities or have elevated plasma levels of natriuretic peptides or cardiac troponin. The first-line treatment of patients with HF with reduced ejection fraction includes foundational therapies with angiotensin receptor–neprilysin inhibitors, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists, sodium–glucose cotransporter 2 (SGLT2) inhibitors and diuretics. The first-line treatment of patients with HF with mildly reduced ejection fraction or with HF with preserved ejection fraction includes SGLT2 inhibitors and diuretics. The timely initiation of these disease-modifying therapies and the optimization of treatment are crucial in all patients with HF. Reassessment after initiation of these therapies is recommended to evaluate patient symptoms, health status and left ventricular function, and timely referral to a HF specialist is necessary if a patient has persistent advanced HF symptoms or worsening HF. Lifestyle modification and treatment of comorbidities such as diabetes mellitus, ischaemic heart disease and atrial fibrillation are crucial through each stage of HF. This Review provides an overview of the management strategies for HF according to disease stages that are derived from the recommendations in the latest US and European HF guidelines.

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Key points

- Patients with cardiovascular risk factors such as hypertension, diabetes mellitus, ischaemic heart disease, obesity, a family history of cardiomyopathies or previous exposure to cardiotoxic agents are considered to be at risk of heart failure (HF) and will benefit from HF screening.
- Patients with stage A pre-HF are those who have developed either structural or functional cardiac abnormalities or have elevated plasma levels of natriuretic peptides or cardiac troponin and who might benefit from close monitoring and early treatment and prevention strategies.
- The first-line treatment of patients with HF with reduced ejection fraction (HFrEF) includes initiation and optimization of foundational therapy with angiotensin receptor–neprilysin inhibitors (ARNIs), angiotensin-converting enzyme inhibitors (ACEIs) (or angiotensin receptor blockers (ARBs) if ACEIs are not tolerated), β-blockers, mineralocorticoid receptor antagonists (MRAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors.
- Additional pharmacological therapies for patients with HFrEF include hydralazine and nitrates in Black patients and consideration of ivabradine, vericiguat and digoxin in selected symptomatic patients.
- Treatment of patients with HF with mildly reduced ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF) now includes SGLT2 inhibitors as first-line therapy; additional therapies include diuretics if congestion is present and consideration of ARNIs, ARBs and MRAs in patients with HFmrEF or HFpEF, and ACEIs or ARBs and β-blockers in patients with HFmrEF.

Introduction

Heart failure (HF) is a major health burden in Western countries, with respect to hospitalizations, mortality and potential years of life lost, similar to that of cancer[1]. By comparison with patients with common types of cancer, patients with HF have very similar case-fatality rates (59% versus 58% within 5 years, respectively) and rates of premature life-years lost[2]. Furthermore, the burden of risk factors associated with HF is increasing owing to rising rates of hypertension, diabetes mellitus and obesity[3]. The lifetime risk of HF has increased to 24%, meaning that approximately one in four individuals will develop HF in their lifetime[4,5]. Furthermore, despite the advances in treatment strategies and an expansion in guideline recommendations for the treatment of HF[6], HF mortality has continued to increase since 2012 (refs. 4,7–9). Together, these findings underline the importance of timely recognition of the risks associated with HF. Furthermore, evolving preventive strategies for patients at risk of HF[6,10] highlight the need to aim for earlier detection and prevention of HF, similar to the approaches used for cancer prevention. This Review provides an overview of the management strategies for HF according to disease stages that are derived from the recommendations in the latest US and European HF guidelines[6,10].

In the Universal Definition and Classification of HF[2] and the 2022 American College of Cardiology (ACC), American Heart Association (AHA) and Heart Failure Society of America (HFSA) guidelines for the management of HF[6], the stages of HF were redefined with a special emphasis on the definition of pre-HF (Fig. 1 and Box 1). The terminology has been updated in these latest guidelines so that each stage is more clearly defined and thus will be better understood by non-specialists and patients. The latest European guidelines on the treatment and management of HF are not organized according to the stages of HF, but several sections of the guidelines specifically address HF prevention, the management of acute decompensated or advanced HF, and the indications for advanced therapies, such as heart transplantation[11].

Stage A HF or at risk of HF

Patients with cardiovascular risk factors such as hypertension, diabetes, ischaemic heart disease or obesity are considered to be at risk of HF and to have stage A HF[2,6,10]. Owing to the high prevalence of hypertension, diabetes and obesity in the general population, approximately one-third of the adult population in the USA can be considered to be at risk of HF or in stage A HF[2,6,10]. In addition to these risk factors, individuals with a family history of genetic or hereditary cardiomyopathies, or those who have been exposed to cardiotoxic agents, are also considered to be at risk of HF. Patients with stage A HF require multidisciplinary management and treatment of their risk factors, close monitoring for the development of HF and might benefit from screening for HF[6].

With regard to the primordial prevention of cardiovascular risk factors, healthy lifestyle habits such as maintaining normal weight, blood pressure and blood sugar levels, consumption of a healthy diet, smoking cessation and participation in regular physical activity are beneficial in reducing the future risk of HF[12–14]. In patients with hypertension, optimal control of blood pressure levels in accordance with the guidelines for the management of hypertension is associated with a significant reduction in the future risk of HF[6]. In patients with type 2 diabetes with established cardiovascular disease or cardiovascular risk factors, treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors has been shown to reduce the risk of HF development or hospitalizations for HF[15–17] and is recommended by HF management guidelines[6]. In patients with obesity, with or without diabetes, treatment with glucagon-like peptide 1 receptor (GLP1R) agonists is associated with significant weight loss[18], but a meta-analysis of studies involving GLP1R agonist treatment in patients with diabetes and without HF suggests that this agent does not alter the risk of future HF events[19,20]. Furthermore, in patients with established HF with reduced ejection fraction (HFrEF), the safety and efficacy of GLP1R agonists are not clear. In patients with chronic HFrEF, treatment with GLP1R agonists has been linked to an increase in heart rate and more severe cardiac adverse events[21] and nominal (albeit nonsignificant) increases in the primary end point of time to death and rehospitalization for HF[22,23]. Interestingly, a large-scale clinical trial published in 2023 showed that in patients with obesity and cardiovascular disease, treatment with the GLP1R agonist semaglutide (administered subcutaneously once per week) was associated with a 20% relative risk reduction in major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) compared with placebo[24–26]. The secondary trial end points included a composite HF end point comprising death from cardiovascular causes or hospitalization or an urgent medical visit for HF. Although the hazard ratio (HR) for the HF composite end point suggested an 18% relative risk reduction in patients who received semaglutide (HR 0.82, 95% CI 0.71–0.96), superiority testing was not performed for the HF end point because the between-group difference with respect to death from cardiovascular causes did not meet the required threshold for hierarchical testing[26].

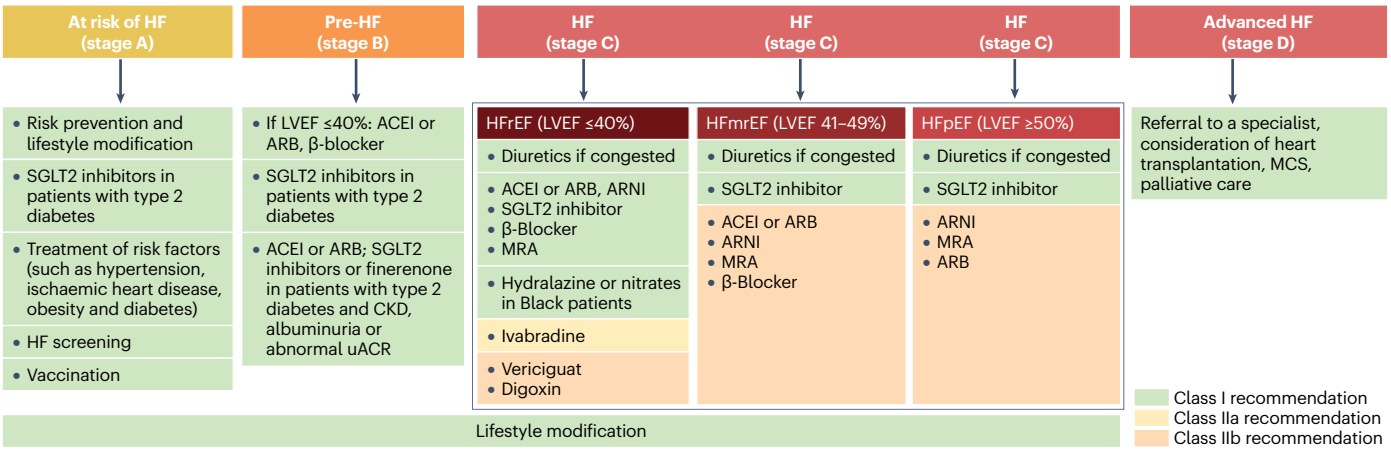
At risk of HF (stage A)
Pre-HF (stage B)
HF (stage C)
HF (stage C)
HF (stage C)
Advanced HF (stage D)
• Risk prevention and lifestyle modification
• SGLT2 inhibitors in patients with type 2 diabetes
• Treatment of risk factors (such as hypertension, ischaemic heart disease, obesity and diabetes)
• HF screening
• Vaccination
• If LVEF ≤40%: ACEI or ARB, β-blocker
• SGLT2 inhibitors in patients with type 2 diabetes
• ACEI or ARB; SGLT2 inhibitors or finerenone in patients with type 2 diabetes and CKD, albuminuria or abnormal uACR
HFrEF (LVEF ≤40%)
• Diuretics if congested
• ACEI or ARB, ARNI
• SGLT2 inhibitor
• β-Blocker
• MRA
• Hydralazine or nitrates in Black patients
• Ivabradine
• Vericiguat
• Digoxin
HFmrEF (LVEF 41–49%)
• Diuretics if congested
• SGLT2 inhibitor
• ACEI or ARB
• ARNI
• MRA
• β-Blocker
HFpEF (LVEF ≥50%)
• Diuretics if congested
• SGLT2 inhibitor
• ARNI
• MRA
• ARB
Referral to a specialist, consideration of heart transplantation, MCS, palliative care
Lifestyle modification
Class I recommendation
Class IIa recommendation
Class IIb recommendation

Fig. 1 | Recommendations for pharmacological therapy across all stages of HF. Pharmacological therapy recommendations for patients at risk of heart failure (HF) (stage A), with pre-HF (stage B), overt HF (stage C) or advanced HF (stage D). Each treatment is colour-coded according to the class of recommendation and level of evidence in HF guidelines[6,42]. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; HFmrEF, HF with mildly reduced ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium–glucose cotransporter 2; uACR, urine albumin-to-creatinine ratio.

Further studies are needed to determine whether weight loss using GLP1R agonists would be safe and associated with a reduced risk of HF.

Stage B pre-HF

Screening

Patients with stage B pre-HF are at higher risk of developing HF and have worse outcomes than patients at risk of HF (stage A HF)[6]. For patients at risk of developing HF (such as those with diabetes, coronary artery disease or hypertension), screening based on the biomarker natriuretic peptide and follow-up with a multidisciplinary care team (including a cardiovascular specialist who prescribes guideline-directed medical therapy (GDMT)) is a class IIa recommendation in the 2022 US HF guidelines[6] (Fig. 1). This recommendation is supported by findings from the STOP HF trial[27], which showed that in patients with cardiovascular risk factors but without HF or left ventricular (LV) dysfunction, yearly screening of plasma natriuretic peptide levels followed by multidisciplinary management significantly reduced the risk of developing HF and LV systolic and diastolic dysfunction. Annual screening using plasma natriuretic peptide measurements is now included as a recommendation in patients with diabetes in the consensus report of the American Diabetes Association[10,27,28].

In addition to biomarker screening, screening for structural or functional cardiac abnormalities via imaging might be beneficial for selected individuals, such as those with obesity in whom plasma natriuretic peptide levels might be low or patients with suspected infiltrative, genetic or hereditary cardiomyopathies. Similarly, in patients being considered for potentially cardiotoxic therapies, measurement of plasma cardiac troponin levels for further risk stratification is included as a class IIb recommendation in the US HF guidelines[6]. Finally, in first-degree relatives of patients with genetic or inherited cardiomyopathies, genetic screening and counselling are recommended[6].

Treatment

The current treatment strategies for patients with stage B pre-HF include continuation of all indicated therapies for patients with stage A pre-HF. These strategies include the treatment and management of hypertension, diabetes, ischaemic heart disease and valvular heart disease according to the guidelines[6]. In addition, in asymptomatic patients with a LV ejection fraction (LVEF) of ≤40%, angiotensin-converting enzyme inhibitors (ACEIs) (or angiotensin receptor blockers (ARBs) if ACEIs are not tolerated) and β-blockers are indicated to prevent the development of symptomatic HF and to reduce mortality[6] (Fig. 1). Although mineralocorticoid receptor antagonists (MRAs) and angiotensin receptor–neprilysin inhibitors (ARNIs) are indicated in patients with symptomatic HFrEF, these agents are not indicated in asymptomatic patients with LV dysfunction[6]. In a randomized clinical trial of patients with acute myocardial infarction complicated by reduced LVEF, pulmonary congestion or both, the ARNI sacubitril–valsartan did not significantly lower the incidence of death from cardiovascular causes or HF compared with the ACEI ramipril[29]. At present, data are lacking on the preventive role of ARNIs in patients with asymptomatic LV dysfunction.

Similarly, SGLT2 inhibitors are currently not indicated for the treatment of asymptomatic LV systolic dysfunction in the absence of diabetes, but are indicated in patients with symptomatic HF across all ejection fraction categories, including HFrEF, HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF)[6,30,31]. An ongoing study is examining the efficacy and safety of SGLT2 inhibitors in patients with myocardial infarction with or without HF or LV dysfunction[32]. However, among patients with type 2 diabetes, SGLT2 inhibitors are indicated in those either with established cardiovascular disease or at high cardiovascular risk[6]. This guideline recommendation is supported by large-scale clinical trial findings that showed a consistent benefit of SGLT2 inhibitors for patients with diabetes for the prevention of HF hospitalization and worsening kidney disease[15–17]. Furthermore, these trials in patients with diabetes showed evidence of HF prevention among patients with or without reduced LVEF who received SGLT2 inhibitors[32], suggesting that patients with pre-HF might also benefit from this drug.

Box 1

Stages of heart failure[2,6]

At risk of HF or stage A
Patients at risk of heart failure (HF), but without current or a history of symptoms or signs of HF, and without structural, biological or genetic markers of heart disease.

Pre-HF or stage B
Patients without current or a history of symptoms or signs of HF, but evidence of either structural heart disease, abnormal cardiac function or elevated plasma levels of natriuretic peptides or cardiac troponin, especially in the setting of exposure to cardiotoxic agents. Other commonly available biomarkers, such as urine albumin-to-creatinine ratio ≥30 mg/g, can also be useful for predicting the risk of developing incident HF[115]. The presence of genetic variants can also be used to identify individuals at a higher risk of HF[116].

Overt HF or stage C
Patients with current or a history of symptoms or signs of HF caused by structural or functional cardiac abnormalities.

Advanced HF or stage D
Patients with severe symptoms or signs of HF at rest, recurrent hospitalizations for HF despite receiving guideline-directed medical therapies, or those with HF that is refractory to or who are intolerant of guideline-directed medical therapies.

All patients with diabetes are at risk of developing HF. In addition to SGLT2 inhibitors, numerous other treatment strategies are available for glycaemic control in patients with diabetes. GLP1R agonists are associated with improvements in major adverse cardiovascular end points, but have not been shown to significantly reduce the rate of HF events[6,33]. At present, no large-scale randomized trials have assessed the efficacy of other antidiabetes agents, such as metformin, in reducing the risk of HF. To determine which patients with diabetes should be treated with SGLT2 inhibitors, patients can be screened for pre-HF by measuring plasma natriuretic peptide levels[6,28] and by imaging, including echocardiography in selected patients (such as those with obesity or suspected structural or functional cardiac abnormalities).

SGLT2 inhibitors are effective in reducing the incidence of end-stage kidney disease, lowering the risk of developing HF and HF hospitalizations, and preventing the decline in estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease (CKD) or albuminuria[34–36]. In the DAPA-CKD trial[36], dapagliflozin significantly reduced the risk of a composite outcome of a sustained decline in eGFR of at least 50%, end-stage kidney disease or death from renal or cardiovascular causes compared with placebo in patients with CKD with or without diabetes. In the 2023 European Society of Cardiology (ESC) guidelines for the management of cardiovascular disease in patients with diabetes, SGLT2 inhibitors are recommended for patients with CKD (both those with and those without diabetes) if eGFR is at least 20–25 ml/min/1.73 m² to reduce the risk of adverse cardiac and renal events[37]. Treatment with ACEIs or ARBs of patients with diabetic nephropathy has also been shown to prevent HF[38,39]. Furthermore, MRA medications have proved effective in preventing albuminuria or HF in certain patient populations, but their role in preventing HF specifically in patients with diabetic nephropathy is not well established. In patients with CKD, albuminuria and type 2 diabetes, the selective, non-steroidal MRA finerenone has been shown to improve cardiorenal outcomes and reduce HF hospitalizations and other HF outcomes[40,41], with consistent benefits across different eGFR or urine albumin-to-creatinine ratio (uACR) categories[41]. In the 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes, finerenone is recommended for patients with CKD and albuminuria associated with type 2 diabetes if eGFR is ≥25 ml/min/1.73 m² and serum potassium is <5.0 mmol/l, to reduce the risk of adverse cardiac and renal events[37]. Therefore, ACEIs, ARBs, SGLT2 inhibitors and finerenone can be beneficial for the patient population with diabetes plus CKD, albuminuria or abnormal uACR.

Beyond pharmacological therapies, in patients who are at least 40 days after myocardial infarction with LVEF ≤30%, are receiving GDMT and have a reasonable probability of meaningful survival past 1 year, an implantable cardioverter–defibrillator (ICD) is a class I recommendation for the primary prevention of sudden cardiac death (SCD)[6].

Similar to patients with stage A pre-HF, lifestyle changes are crucial to prevent HF in patients with stage B pre-HF[6], including regular physical activity, consumption of a heart-healthy diet, optimal control of blood pressure and cholesterol levels and avoidance of tobacco and excessive alcohol consumption[6]. In addition, patients with pre-HF should be closely monitored and should attend regular follow-up appointments with clinicians. Finally, in patients with non-ischaemic cardiomyopathies with arrhythmias or structural and functional cardiac abnormalities that might be attributable to genetic or hereditary cardiomyopathies, genetic testing and counselling are also recommended[6].

Stage C symptomatic HF

In the 2022 USA HF guidelines, recommendations for the treatment of symptomatic HF are structured according to LVEF classification, partly owing to the available clinical trial evidence, which defines HF phenotypes according to LVEF[6]. In the US guidelines and the Universal Definition of HF report, HFrEF is defined as LVEF ≤40%, HFmrEF as LVEF 41–49% and HFpEF as LVEF ≥50%[2,6] (Fig. 1). A new LVEF classification — HF with improved ejection fraction (HFimpEF) — was also introduced. This category defines patients with a historical baseline LVEF in the HFrEF range (≤40%) and a subsequent LVEF that increased to >40%. The treatment strategies for each LVEF subclassification are discussed in the sections below.

Step 1: initiation of quadruple therapy

According to the ACC and the ESC HF guidelines, initiation of quadruple therapy with renin–angiotensin–aldosterone system (RAAS) inhibitors (including ARNIs or ACEIs or ARBs), β-blockers, MRAs and SGLT2 inhibitors is recommended as the first step in the treatment of patients with HFrEF[6,11,42] (Fig. 2). Robust evidence from large-scale clinical trials has shown that these agents can reduce the risk of cardiovascular death and HF hospitalization as early as within 30 days of drug initiation[43–45], underlining the importance of timely treatment initiation. Treatment with SGLT2 inhibitors[44,45] or ARNIs[46] can also slow the decline in eGFR and lead to improvements in quality of life[47–49]. In addition to the known effects of reversal of LV remodelling with β-blockers[50–53], ACEIs[54] or MRAs[6,55], evidence suggests that treatment

with ARNIs[56,57] (and to a modest extent with SGLT2 inhibitors[58,59]) can reverse LV remodelling, exemplified by a reduction in LV volume and an increase in LVEF[56,57]. In patients with HFrEF, clinical trial findings from the past 5 years revealed an incremental benefit in reducing the risk of cardiovascular death and HF hospitalization when SGLT2 inhibitors or ARNIs are added to background therapy[43–45]. Furthermore, according to a systematic network meta-analysis, the estimated aggregate benefit was greatest for a combination of quadruple therapy with ARNIs, β-blockers, MRAs and SGLT2 inhibitors[60].

In the ACC–AHA–HFSA guidelines, the use of ARNIs is recommended either as replacement therapy in patients with chronic HFrEF with New York Heart Association (NYHA) class II or III symptoms who can tolerate an ACEI or ARB; or as a de novo treatment in patients with HFrEF with NYHA class II or III symptoms, including those who have not been treated with an ACEI[6]. Although data are limited in patients with chronic HF, the US guidelines recommend the use of an ARNI as a de novo treatment for patients with symptomatic HFrEF to simplify their management[6]. The de novo treatment recommendation is supported by evidence of beneficial effects of ARNIs, such as the reduction in plasma N-terminal pro-B-type natriuretic peptide levels and a reduction in adverse LV remodelling compared with treatment with ACEIs or ARBs in patients hospitalized with HF[6,43,61–63]. In the 2021 ESC HF guidelines, an ARNI is recommended as a replacement for an ACEI in suitable patients who remain symptomatic despite treatment with ACEIs, β-blockers and MRAs, and is also suggested as a possible first-line drug[11].

According to the US guidelines, quadruple therapy can be initiated simultaneously at low doses in selected patients[6]. The initiation of all four drugs at the same time might not be feasible in all patients, but they can be initiated sequentially, with the sequence being guided by clinical or other factors, but without the need to achieve target dosing before starting the next drug[6]. Of note, ARNIs should not be administered concomitantly with ACEIs, or within 36 h of the last dose of an ACEI, owing to an increased risk of angio-oedema. Furthermore, ARNIs or ACEIs should not be administered to patients with a history of angio-oedema[6].

In patients with HF who have evidence of fluid retention, diuretics are also recommended, regardless of LVEF, to relieve congestion, improve symptoms and prevent the worsening of HF[6,11]. In the US guidelines, addition of a thiazide (such as metolazone) is recommended only for patients who do not respond to moderate-dose or high-dose loop diuretics to minimize electrolyte abnormalities[6].

Individualization of quadruple therapy drug sequence. Importantly, regardless of the order of initiation or sequence, timely initiation (within 4–6 weeks of diagnosis) of all four classes of medication is important for favourable clinical outcomes in patients with HFrEF. However, patient characteristics, such as haemodynamic profile, NYHA class, HF aetiology and comorbidities, are important in determining the sequence of quadruple drug therapy. SGLT2 inhibitors and MRAs might be preferred for earlier initiation after diuretics in patients with substantial congestion and volume overload, whereas SGLT2 inhibitors and ARNIs might be considered for earlier initiation in patients with HFrEF and CKD owing to the beneficial effects of these drugs in slowing the decline in eGFR[46,64,65]. In patients with hyperkalaemia, SGLT2 inhibitors or ARNIs might be preferred for earlier initiation over MRAs or ACEIs, and earlier initiation of SGLT2 inhibitors or ARNIs might allow for subsequent initiation and continuation of MRAs[66]. In patients with HF who experience hyperkalaemia (serum potassium level ≥5.5 mEq/l) when taking a RAAS inhibitor, the effectiveness of potassium binders remains uncertain and requires further research[6]. Patients with active myocardial ischaemia, recent myocardial infarction or atrial or ventricular arrhythmia might benefit from earlier initiation of β-blockers. SGLT2 inhibitors are indicated in patients with HF and diabetes[6,11], regardless of LVEF. Furthermore,

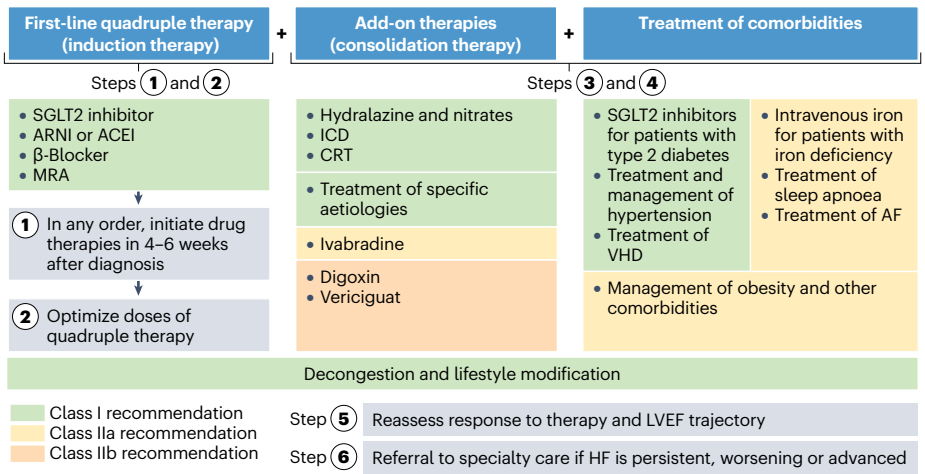
First-line quadruple therapy (induction therapy)
+
Add-on therapies (consolidation therapy)
+
Treatment of comorbidities
Steps 1 and 2
Steps 3 and 4
• SGLT2 inhibitor
• ARNI or ACEI
• β-Blocker
• MRA
1 In any order, initiate drug therapies in 4–6 weeks after diagnosis
2 Optimize doses of quadruple therapy
• Hydralazine and nitrates
• ICD
• CRT
• Treatment of specific aetiologies
• Ivabradine
• Digoxin
• Vericiguat
• SGLT2 inhibitors for patients with type 2 diabetes
• Treatment and management of hypertension
• Treatment of VHD
• Intravenous iron for patients with iron deficiency
• Treatment of sleep apnoea
• Treatment of AF
• Management of obesity and other comorbidities
Decongestion and lifestyle modification
Class I recommendation
Class IIa recommendation
Class IIb recommendation
Step 5 Reassess response to therapy and LVEF trajectory
Step 6 Referral to specialty care if HF is persistent, worsening or advanced

Fig. 2 | Stepwise initiation and optimization of pharmacological therapy and indicated device therapy for patients with HFrEF. Step 1 involves the initiation of first-line quadruple therapy with sodium–glucose cotransporter 2 (SGLT2) inhibitors, angiotensin receptor–neprilysin inhibitors (ARNIs) or angiotensin-converting enzyme inhibitors (ACEIs) (or angiotensin receptor blockers (ARBs) if ACEIs are not tolerated), β-blockers and mineralocorticoid receptor antagonists (MRAs). Step 2 involves the optimization of quadruple therapy. Steps 3 and 4 include consideration of additional therapies, such as hydralazine and nitrates in Black patients, and ivabradine, vericiguat and device therapies (including implantable cardioverter–defibrillator (ICD) and cardiac resynchronization therapy (CRT)). Steps 5 and 6 include reassessment of patient health status, cardiac function and laboratory and other diagnostic markers to determine response to therapies and trajectory of left ventricular ejection fraction (LVEF). If the patient demonstrates persistent, worsening or advanced heart failure (HF) symptoms, referral to a specialty HF centre is recommended. Each treatment is colour-coded according to the class of recommendation and level of evidence in HF guidelines[6,42]. AF, atrial fibrillation; HFrEF, HF with reduced ejection fraction; VHD, valvular heart disease.

earlier initiation of ACEIs, instead of ARNIs, might be preferred in patients with NYHA class IV symptoms, given the findings from the LIFE trial, which showed that patients with advanced HF and NYHA class IV symptoms treated with ARNIs had numerically higher (albeit not significant) rates of HF events than patients treated with ACEIs[67,68]. This finding suggests that neprilysin inhibition might not be effective in patients with advanced HF with NYHA class IV symptoms. Accordingly, in the ACC–AHA–HFSA HF guidelines, an ARNI is recommended only in patients with NYHA functional class II–III HF[6]. By contrast, in the ESC guidelines, ARNI treatment is recommended in all symptomatic patients with HFrEF[11].

Beyond the specific phenotypes already mentioned, other factors might also limit the initiation of certain drugs for patients with stage C HF. For example, substantial symptomatic bradycardia could be a contraindication for the initiation of β-blockers, severe hypotension might be a challenge for the initiation of an ARNI and preshock or shock could preclude the initiation of quadruple therapy until haemodynamic stability is achieved. In patients with HFrEF, MRA therapy is recommended if the eGFR is >30 ml/min/1.73 m^2 and serum potassium level is <5.0 mEq/l. Careful monitoring of potassium levels, renal function and diuretic dosing should be performed after initiation of MRA, especially in patients with CKD or those at risk of hyperkalaemia[6,11].

Early initiation of quadruple therapy. Clinical trial evidence shows the benefit of initiation of SGLT2 inhibitors[44] or ARNIs[43] in patients with HFrEF as early as within the first 30 days of diagnosis, or the initiation of SGLT2 inhibitors in patients with HFmrEF or HFpEF within 2 weeks of diagnosis[69]. Quadruple therapy should thus be optimally initiated within the first 4–6 weeks after a diagnosis of HF. In other diseases, such as cancer, the first standard treatment is usually defined as induction therapy. The disease-modifying effects of quadruple therapy in HF seem to fit the characteristics of a first-line, disease-modifying induction therapy. Given the similar mortality between HF and common forms of cancer, timely initiation of quadruple therapy in patients with HFrEF might be important in theory, similar to the importance of the timely initiation of induction chemotherapy in patients with cancer[70] (Fig. 2).

In patients who are hospitalized with HF, evidence shows that GDMT can be initiated safely in patients before hospital discharge[30,71–73]. Real-world data demonstrate only minimal changes in GDMT use in the year after hospital discharge, highlighting the need to consider earlier and greater implementation of GDMT to manage risks[9]. In both the US and European guidelines, the initiation of GDMT after clinical stability in patients hospitalized for HF is a class I recommendation[6,42]. On the basis of randomized clinical trial findings that demonstrated safety and efficacy in reducing hospital readmission for HF or all-cause death[71], the latest ESC HF guidelines recommend a high-intensity care approach, which involves initiation and rapid uptitration of oral HF therapies in patients hospitalized with HF, followed by close monitoring in the first 6 weeks after hospital discharge[42].

Numerous models of care exist in the initiation and optimization of GDMT, including multidisciplinary care coordination, telehealth and remote monitoring, and face-to-face visits[74]. Patients with HF should receive education and care from multidisciplinary teams to facilitate the implementation of GDMT, address potential barriers to self-care, lower the risk of subsequent rehospitalizations for HF and reduce the risk of death[6]. Given that newer HF therapies, such as SGLT2 inhibitors and ARNIs, can facilitate the initiation of other GDMTs, such as MRAs, and have favourable effects on kidney function and potassium levels, optimization of GDMT by combination and addition of oral medications has been shown to be safe[6,74].

Step 2: optimizing doses of the foundational therapies

According to the US HF guidelines, after initiation of quadruple therapy, drug doses should be increased to target levels, if tolerated[6] (Fig. 2). In patients with HF, a greater clinical benefit has been shown with optimal doses of β-blockers[75] and ACEIs[76], when compared with lower doses. Evolving evidence suggests similar benefits between moderate doses of ARNIs and MRAs[77]. Furthermore, in patients with HFrEF, newer agents such as ARNIs[57,77] and SGLT2 inhibitors[58], as well as older agents such as β-blockers[77], have been shown to reverse the cardiac remodelling process, whereas a reduction in SCD has been observed with use of these newer agents[60,78]. These findings highlight the importance of GDMT drug dosing in striving for maximal benefits and that GDMT dose should be optimized before consideration of device therapies, such as ICDs. According to the US HF guidelines, the titration and optimization of GDMT should be considered as frequently as every 1–2 weeks depending on the patient's symptoms, vital signs and laboratory findings[6].

Importantly, not all GDMTs require multiple steps for uptitration. SGLT2 inhibitors are recommended as a single standard dose and do not require uptitration. MRA uptitration might involve only one step to achieve the target dose, whereas β-blockers, ACEIs, ARBs and ARNIs might require two or three steps.

Step 3: addition of indicated oral therapies to foundational therapy

After initiation and optimization of the doses of quadruple therapy, additional oral therapies can be considered in certain subgroups of patients with symptomatic HFrEF to reduce symptom severity and adverse outcomes (Fig. 2). Hydralazine and nitrates are indicated in Black patients with HFrEF and NYHA class III–IV symptoms[6,79]. In patients with symptomatic stable chronic HFrEF with a heart rate of ≥70 bpm in sinus rhythm despite β-blocker treatment, ivabradine treatment can be beneficial to reduce HF hospitalizations and cardiovascular death[6,11]. Furthermore, addition of digoxin to GDMT for patients with symptomatic HFrEF might be considered to reduce the risk of HF hospitalization[6]. Finally, in selected high-risk patients with HFrEF and recent worsening of HF, vericiguat, an oral soluble guanylate cyclase stimulator, might be considered to reduce HF hospitalizations and cardiovascular death[6,11,80].

Important considerations for additional oral therapies after initiation and optimization of GDMT include treatment for comorbidities such as iron deficiency, atrial fibrillation, ischaemic heart disease, valvular heart disease, sleep apnoea and diabetes, in addition to the treatment of specific HF aetiologies, such as cardiac amyloidosis or sarcoidosis[6,11]. In patients with HFrEF and hypertension, uptitration of GDMT to the maximally tolerated target dose is recommended to reduce cardiovascular events[6]. In patients with HF and type 2 diabetes, the use of SGLT2 inhibitors is recommended for the management of diabetes and to reduce HF-related morbidity and mortality[6,11].

Treatment of iron deficiency. In patients with HFrEF and iron deficiency with or without anaemia, intravenous iron replacement is associated with improvements in quality of life, 6-min walking distance, exercise performance, NYHA class and HF symptoms[81–84]. In a meta-analysis of studies in patients with HFrEF and iron deficiency, intravenous ferric carboxymaltose was associated with a significantly reduced risk of hospital admissions for HF and other cardiovascular

causes compared with placebo[85]. However, in a 2023 large-scale clinical trial involving ambulatory patients with HFrEF and iron deficiency, no differences were observed between ferric carboxymaltose treatment and placebo with respect to the hierarchical composite end point of death, HF hospitalizations or 6-min walking distance[84]. In the US HF guidelines, intravenous iron therapy is considered a reasonable treatment (class IIa recommendation) to improve functional status and quality of life in patients with HFrEF[6]. By contrast, in the ESC guidelines, a class I, level of evidence (LOE) A recommendation is given for the use of intravenous iron to reduce symptoms and improve quality of life[42]. The ESC guidelines also include a class II, LOE A recommendation for the use of intravenous iron to reduce HF hospitalizations[42]. Eythropoietin-stimulating agents are not recommended in patients with HF and anaemia owing to the associated risk of thrombo-embolic complications and the lack of efficacy[6].

Step 4: reassess symptoms and LVEF, and consider device therapy

In addition to oral therapies, indicated device therapies, such as ICD or cardiac resynchronization therapy (CRT), should be considered in patients with HFrEF[6,11]. After optimization of GDMT, patients will probably show improvements in symptoms, LVEF and LV volume. Therefore, LVEF assessment should be repeated before consideration of device therapies. This reassessment can be conducted 3 months after the optimization of GDMT, as suggested by the ESC HF guidelines[11]. Of note, however, the timing of ICD or CRT should be individualized; patients at high risk of SCD, such as those with arrhythmogenic cardiomyopathy, might require earlier considerations for ICD.

In patients with LVEF <35% and NYHA class II or III symptoms who are receiving long-term GDMT and who have a reasonable expectation of meaningful survival past 1 year, the use of ICDs is recommended for the primary prevention of SCD[6]. The US guidelines give a high-level recommendation for ICD use in all patients with LVEF <35% and NYHA class I–III symptoms (class I, LOE A)[6], whereas the ESC guidelines provide a high-level (class I) recommendation only for patients with ischaemic cardiomyopathy and a lower recommendation (class II, LOE A) for patients with non-ischaemic cardiomyopathy[11]. For patients with HF receiving GDMT who have LVEF ≤35%, left bundle branch block (LBBB) with a QRS duration of ≥150 ms, NYHA class II, III or ambulatory IV symptoms and are in sinus rhythm, CRT is indicated to reduce the risk of death and hospitalization, and to improve symptoms and quality of life[6,11]. In patients with HFrEF with other cardiac conduction abnormalities, such as a non-LBBB pattern with a QRS duration of ≥150 ms or LBBB with a QRS duration of <150 ms, CRT can similarly be effective in reducing total mortality and hospitalizations, and in improving symptoms and quality of life[6,11].

Patients with HF and valvular heart disease should be managed by a multidisciplinary team in accordance with clinical practice guidelines for valvular heart disease to prevent worsening of HF and adverse clinical outcomes. Severe aortic stenosis, aortic valve regurgitation, mitral valve regurgitation and tricuspid valve regurgitation require timely assessment, optimization of GDMT and consideration of surgical or transcatheter interventions. Transcatheter edge-to-edge mitral valve repair can be considered in symptomatic patients with HFrEF and severe functional mitral regurgitation with suitable anatomy, LVEF 20–50% and LV end-systolic dimension <70 mmHg after optimization of GDMT[6].

Device-based interventions for the treatment of HF are constantly evolving and their use alongside GDMT should be routinely reassessed[86–89]. Multidisciplinary shared decision-making with patients with HF on the benefits and potential risks of device therapies is crucial.

Step 5: reassess symptoms, health status and therapy response

The use of GDMT in patients with HFrEF has been shown to reduce HF hospitalizations and cardiovascular death[6,11] as well as improve symptom severity, functional capacity (such as NYHA class) and quality of life[6,49]. In patients with HFrEF, treatment with β-blockers, MRAs, ARNIs, ACEIs and SGLT2 inhibitors has been associated with favourable changes in LV volume, LV mass and LVEF, which suggests a reversal in LV remodelling[6,56,58]. Furthermore, exercise performance can also improve with GDMT[6,44,90,91]. Therefore, the symptoms, health status and functional class of patients after treatment with GDMT warrants reassessment and is recommended by the US HF guidelines[6]. Of note, approximately 10–20% of patients might not respond favourably to GDMT and might even experience worsening of HF[92]. Worsening HF has been defined in the guidelines as an increase in symptoms or signs and a decline in functional capacity, as well as the increased need for escalation of therapies (such as intravenous or other advanced therapies) and hospitalization[2,6]. Patients who do not respond to GDMT might have persistent HF with active symptoms and signs that might become more severe with time, abnormal biomarkers that are indicative of end-organ damage (including elevated plasma natriuretic peptide levels) and persistent ventricular dysfunction and remodelling that does not improve with time[93].

Step 6: referral for advanced HF therapies for stage D HF

Patients with worsening HF despite optimal GDMT who have clinical indicators of advanced (stage D) HF, such as recurrent HF hospitalizations, need for intravenous vasoactive drugs and escalation of diuretics, intolerance to GDMT, persistently elevated natriuretic peptide levels, end-organ dysfunction, low LVEF, defibrillator shocks, hypotension and ventricular tachyarrhythmia, should be referred to a HF specialist. Timely referral for review and consideration of advanced HF therapies, including mechanical circulatory support, cardiac transplantation and palliative care, is crucial to achieve optimal patient outcomes[6,11,94,95]. The median survival time for patients with stage D HF without advanced therapies is <2 years, whereas life expectancy after undergoing cardiac transplantation is >12 years[94].

Other HF phenotypes

HFmrEF. In patients with HFmrEF (LVEF 41–49%), the aetiology of their HF and the trajectory of their LVEF should be established. This subpopulation of patients with HF might show a disease trajectory of active worsening from HFpEF towards HFrEF, or an improvement from HFrEF to HFimpEF. Given that this patient subpopulation might also include patients with ischaemic heart disease, infiltrative cardiomyopathies (such as cardiac amyloidosis), valvular heart disease or myocardial injury, establishing disease aetiology is important to tailor treatment strategies accordingly. Of note, patients with HFmrEF with LVEF in the lower ranges might respond to medical therapies similarly to patients with HFrEF and might thus require similar treatment strategies (Fig. 3).

The DELIVER[30] and EMPEROR-Preserved[31] trials reported reductions in cardiovascular mortality and HF hospitalizations with SGLT2 inhibitor treatment compared with placebo in patients with HF and LVEF >40%, including patients with HFmrEF. On the basis of these findings, SGLT2 inhibitors are now recommended in patients with HFmrEF (class I indication) in the 2023 update of the ESC HF guidelines[42] (Fig. 3).

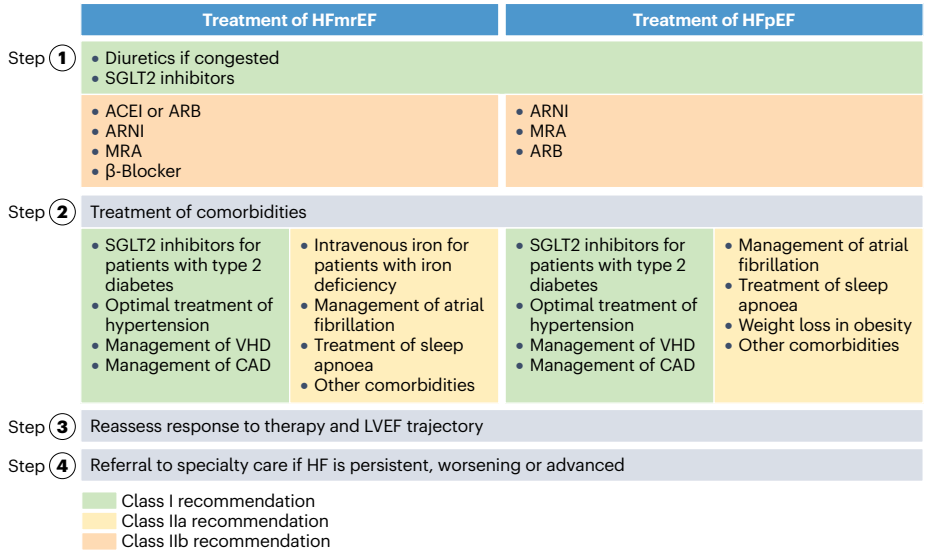
Treatment of HFmrEF
Treatment of HFpEF
Step 1
• Diuretics if congested
• SGLT2 inhibitors
• ACEI or ARB
• ARNI
• MRA
• β-Blocker
• ARNI
• MRA
• ARB
Step 2
Treatment of comorbidities
• SGLT2 inhibitors for patients with type 2 diabetes
• Optimal treatment of hypertension
• Management of VHD
• Management of CAD
• Intravenous iron for patients with iron deficiency
• Management of atrial fibrillation
• Treatment of sleep apnoea
• Other comorbidities
• SGLT2 inhibitors for patients with type 2 diabetes
• Optimal treatment of hypertension
• Management of VHD
• Management of CAD
• Management of atrial fibrillation
• Treatment of sleep apnoea
• Weight loss in obesity
• Other comorbidities
Step 3
Reassess response to therapy and LVEF trajectory
Step 4
Referral to specialty care if HF is persistent, worsening or advanced
Class I recommendation
Class IIa recommendation
Class IIb recommendation

Fig. 3 | Stepwise initiation and optimization of pharmacological therapy and indicated device therapy in patients with HFmrEF or HFpEF. Step 1 involves initiation of sodium–glucose cotransporter 2 (SGLT2) inhibitors and diuretics if the patient is congested. In patients with heart failure (HF) with mildly reduced ejection fraction (HFmrEF), step 2 includes the addition of angiotensin receptor–neprilysin inhibitors (ARNIs) or angiotensin-converting enzyme inhibitors (ACEIs) (or angiotensin receptor blockers (ARBs) if ACEIs are not tolerated), β-blockers or mineralocorticoid receptor antagonists (MRAs) and management of comorbidities. In patients with HF with preserved ejection fraction (HFpEF), step 2 includes addition of ARNIs or MRAs or ARBs and management of comorbidities. For patients with HFmrEF or HFpEF, step 3 includes reassessment of patient health status, cardiac function and laboratory and other diagnostic markers to determine response to therapies and trajectory of left ventricular ejection fraction (LVEF). Step 4 involves referral to specialty HF care if the patient demonstrates persistent and advanced HF symptoms or worsening HF. Indicated therapies are colour-coded according to the class of recommendation and level of evidence in HF guidelines[6,42]. CAD, coronary artery disease; VHD, valvular heart disease.

Post-hoc and subset analyses of clinical trials in patients with HFrEF suggest a potential benefit with the use of other GDMTs (including β-blockers, ARNIs, ACEIs or ARBs, and MRAs) in patients with HFmrEF to reduce the risk of HF hospitalization and cardiovascular death, particularly among patients with LVEF in the lower ranges[6,96–102] (Fig. 2). Given that the evidence of benefit was derived from post-hoc and secondary end-point analyses of existing trials, the use of ARNIs, ACEIs, ARBs, MRAs or β-blockers was given a class IIb indication for patients with HFmrEF in the US guidelines[6].

HFpEF. During the past two decades, many clinical trials have shown no improvement in cardiovascular outcomes in patients with HFpEF who were treated with drugs that were effective in patients with HFrEF[103]. However, as mentioned above, the DELIVER[30] and EMPEROR-Preserved[31] trials showed improvements in cardiovascular mortality and HF hospitalizations with SGLT2 inhibitor treatment among patients with HF with LVEF >40%. At the time of publication of the ACC–AHA–HFSA HF guidelines, only the results from the EMPEROR-Preserved trial[31] had been reported. In this trial, empagliflozin reduced the combined risk of cardiovascular death and HF hospitalization in patients with HFpEF compared with placebo. On the basis of this finding, SGLT2 inhibitors were given a class IIa indication for the treatment of patients with HFmrEF or HFpEF in the US guidelines[6]. The subsequent DELIVER trial[30] demonstrated that dapagliflozin also reduced the combined risk of worsening HF or cardiovascular death in patients with HFmrEF or HFpEF compared with placebo. A consistent benefit was observed across all subgroups of LVEF, including patients with HFmrEF (LVEF 40–50%), HF with normal LVEF (LVEF 50–60%) or even HF with supra-normal LVEF (LVEF >60%)[30]. Accordingly, SGLT2 inhibitors were given a higher class I indication for the treatment of patients with HFmrEF or HFpEF in the 2023 ESC update of the HF guidelines[42] (Fig. 3).

Similar to HFmrEF, the evidence for benefits of ARNIs, ARBs and MRAs for patients with HFpEF was limited to post-hoc and secondary end-point analyses of existing trials; these agents were thus given class IIb recommendations in the US guidelines[6]. Of note, β-blockers are not recommended in patients with HFpEF, owing to the lack of evidence of benefit[6] (Fig. 3).

HFimpEF. This category denotes patients with a baseline LVEF of ≤40% who show an improvement in LVEF (>40%) upon a second measurement[2]. This improvement is usually attributable to GDMT or the treatment of an underlying aetiology of HF[56,58]. These patients, however, should not be categorized as having HFpEF, even if their subsequent LVEF is >50% after treatment. In the DELIVER trial[30], which assessed the efficacy of dapagliflozin in patients with HFmrEF or HFpEF, 18% of the enrolled patients fulfilled the criteria as having HFimpEF at baseline, and treatment with SGLT2 inhibitors was associated with a significant reduction in cardiovascular death and HF hospitalizations compared with placebo among these patients.

The TRED-HF trial[104] enrolled asymptomatic patients who recovered from dilated cardiomyopathy after receiving GDMT for HF, which was demonstrated by an improvement in LVEF (from <40% to ≥50%) and normalization of LV end-diastolic volume. In these patients, withdrawal of GDMT was associated with recurrence of symptoms or the development of LV dysfunction, which suggests that a substantial proportion of patients with HFimpEF might actually be patients in remission rather

than those with full recovery[104]. In the US HF guidelines, continuation of GDMT in patients with HF is recommended to prevent relapse of HF and LV dysfunction, even if patients experience symptom resolution or an increase in LVEF after treatment[6].

HF and obesity. The prevalence of HFpEF is increasing, and patients with HFpEF and obesity have a high HF symptom burden and cardiac functional impairment. In these patients, caloric restriction and aerobic exercise training can result in weight loss and an improvement in exercise capacity[105]. Observational studies have also linked bariatric surgery with substantial weight loss and favourable cardiovascular outcomes in patients with HF[106,107]. Although certain drugs have been approved for weight loss in patients with obesity with or without diabetes, no drugs have been approved to target obesity specifically in patients with HFpEF or HFrEF[108]. In the STEP-HFpEF trial[109] involving patients with HFpEF and obesity, a weekly dose of subcutaneously administered semaglutide resulted in greater reductions in HF symptoms and physical limitations, improvements in exercise function and greater weight loss compared with placebo. Of note, although the magnitude of benefit was directly related to the extent of weight loss[108], the concomitant reductions in plasma natriuretic peptide and C-reactive protein levels with semaglutide suggest potential benefits of the drug beyond just weight loss. Furthermore, in a trial involving patients who were hospitalized for HFrEF, treatment with liraglutide did not improve outcomes compared with placebo[22]. A separate study reported that liraglutide treatment did not alter LV systolic function in patients with stable chronic HF with or without diabetes, but was associated with an increase in heart rate and adverse cardiac events[21]. Together, these findings highlight the need for further studies to establish the safety and efficacy of GLP1R agonists for the management of diabetes or obesity in patients with HFrEF.

Treating congestion in symptomatic HF. Congestion is associated with adverse outcomes in patients with HF regardless of LVEF, and successful decongestion results in more favourable outcomes in ambulatory and hospitalized patients with HF[110,111]. To date, no randomized clinical trials have demonstrated the efficacy of decongestion in improving clinical outcomes and survival in patients with HF and fluid retention, but diuretics are recommended to relieve congestion, improve symptoms and prevent the worsening of HF[6,11]. The addition of a thiazide, such as metolazone, to treatment with a loop diuretic can be considered for patients who do not respond to moderate-dose or high-dose loop diuretics[6]. In hospitalized patients with HF who show evidence of congestion and fluid overload, intravenous loop diuretics are recommended to improve symptoms and reduce morbidity. Diuretics and other GDMTs should be titrated with a goal of relieving congestion to reduce symptoms and risk of rehospitalization. The ADVOR study[112] reported that the addition of acetazolamide to loop diuretic therapy in patients with acute decompensated HF increased the likelihood of successful decongestion, but whether such a diuretic combination therapy can improve clinical outcomes is unknown and requires further research.

Treatment of specific HF aetiologies

Cardiac amyloidosis

Cardiac amyloidosis is increasingly being recognized as a common aetiology of HF that is associated with poor outcomes[113]. However, GDMT for HF might be poorly tolerated in patients with cardiac amyloidosis. Specifically, β-blockers might worsen HF symptoms because they can reduce cardiac output and heart rate. Digoxin can bind to amyloid fibrils and thus patients with amyloidosis have an increased risk of digoxin toxicity, even when the drug concentration in the serum is within the normal range. Finally, drugs that can cause hypotension, such as ARNIs, ACEIs, ARBs or MRAs, might not be well tolerated in patients with cardiac amyloidosis-related HF.

Disease-modifying therapies, including transthyretin (TTR) silencers that disrupt hepatic TTR synthesis via *TTR* mRNA inhibition or degradation, TTR stabilizers that prevent misfolding and deposition of TTR and TTR disruptors that target the tissue clearance of TTR, are being studied in patients with HF. In the randomized ATTR-ACT study[114] involving patients with TTR amyloid cardiomyopathy, the TTR stabilizer tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations, and it slowed the decline in functional capacity and quality of life compared with placebo. In the US HF guidelines, tafamidis is recommended in selected patients with wild-type or variant *TTR* cardiac amyloidosis and HF symptoms to reduce cardiovascular morbidity and mortality[6]. Patients with light-chain cardiac amyloidosis should be referred promptly to a haematology–oncology team for timely initiation of treatment.

Other HF aetiologies

Other HF aetiologies include tachycardia-induced cardiomyopathies, viral myocarditis, peripartum cardiomyopathy, genetic cardiomyopathies, valvular heart disease, cardiac sarcoidosis, cardiotoxicity-related cardiomyopathies, and metabolic, autoimmune or inflammatory cardiomyopathies, all of which might require specific treatment strategies in addition to or beyond standard GDMT for HF. These aetiologies should be identified and targeted therapies should be administered in these patients.

Conclusions

Comprehensive treatment strategies for patients with HFrEF can be similar to treatment approaches for other diseases, such as cancer. The initiation of guideline-directed quadruple therapy in patients with HFrEF can improve symptoms, quality of life and clinical outcomes, including a reduction in cardiovascular death and HF hospitalizations, and corresponds to the concept of induction therapy in patients with cancer. However, this approach alone is not adequate, given that a substantial proportion of patients with HFrEF have a residual risk of death and morbidity despite receiving GDMT. Patients who remain symptomatic require further therapy optimization and addition of other drug therapies, such as hydralazine and nitrates in Black patients, as well as device therapies (ICD or CRT). These additional therapies are similar in concept to 'consolidation therapies' for other diseases, such as cancer, which aim to consolidate the gains obtained, with an intention to further improve outcomes. Likewise, akin to the 'maintenance therapies' that are recommended for cancer, the continuation of GDMT is recommended in patients with HF to prevent disease relapse and LV dysfunction, even if patients show signs of symptom resolution or an improvement in LVEF[6]. Finally, SGLT2 inhibitor treatment is indicated in patients with pre-HF or HF across the full spectrum of LVEF or disease stage (A–D). In patients with HFmrEF or HFpEF, SGLT2 inhibitors are indicated as first-line therapy to reduce cardiovascular mortality and HF hospitalizations[42]. With these strategies, we envision earlier HF detection and initiation of therapy, which will translate into prevention of HF progression, improvements in symptoms and quality of life, and a reduction in mortality and morbidity.

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References

1. Stewart, S., Ekman, I., Ekman, T., Oden, A. & Rosengren, A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). *Circ. Cardiovasc. Qual. Outcomes* **3**, 573–580 (2010).
2. Bozkurt, B. et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J. Card. Fail.* **27**, 387–413 (2021).
3. Tsao, C. W. et al. Heart disease and stroke statistics-2023 update: a report from the American Heart Association. *Circulation* **147**, e93–e621 (2023).
4. Bozkurt, B. Heart failure epidemiology and outcomes statistics. *J. Card. Fail.* **29**, 1412–1451 (2023).
5. Vasan, R. S., Enserro, D. M., Beiser, A. S. & Xanthakis, V. Lifetime risk of heart failure among participants in the Framingham study. *J. Am. Coll. Cardiol.* **79**, 250–263 (2022).
6. Heidenreich, P. A. et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **79**, e263–e421 (2022).
7. Siddiqi, T. J. et al. Trends in heart failure-related mortality among older adults in the United States from 1999-2019. *JACC Heart Fail.* **10**, 851–859 (2022).
8. Jain, V. et al. Demographic and regional trends of heart failure-related mortality in young adults in the US, 1999-2019. *JAMA Cardiol.* **7**, 900–904 (2022).
9. Bozkurt, B. et al. Mortality, outcomes, costs, and use of medicines following a first heart failure hospitalization: EVOLUTION HF. *JACC Heart Fail.* **11**, 1320–1332 (2023).
10. Bozkurt, B. It is time to screen for heart failure: why and how? *JACC Heart Fail.* **10**, 598–600 (2022).
11. McDonagh, T. A. et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **42**, 3599–3726 (2021).
12. Del Gobbo, L. C. et al. Contribution of major lifestyle risk factors for incident heart failure in older adults: the cardiovascular health study. *JACC Heart Fail.* **3**, 520–528 (2015).
13. Hu, G., Jousilahti, P., Antikainen, R., Katzmarzyk, P. T. & Tuomilehto, J. Joint effects of physical activity, body mass index, waist circumference, and waist-to-hip ratio on the risk of heart failure. *Circulation* **121**, 237–244 (2010).
14. Uijl, A. et al. Risk for heart failure: the opportunity for prevention with the American Heart Association's Life's Simple 7. *JACC Heart Fail.* **7**, 637–647 (2019).
15. Zinman, B. et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* **373**, 2117–2128 (2015).
16. Neal, B. et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N. Engl. J. Med.* **377**, 644–657 (2017).
17. Wiviott, S. D. et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **380**, 347–357 (2019).
18. Pi-Sunyer, X. et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N. Engl. J. Med.* **373**, 11–22 (2015).
19. Marso, S. P. et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **375**, 311–322 (2016).
20. Marso, S. P. et al. Effects of liraglutide on cardiovascular outcomes in patients with diabetes with or without heart failure. *J. Am. Coll. Cardiol.* **75**, 1128–1141 (2020).
21. Jorsal, A. et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE) — a multicentre, double-blind, randomised, placebo-controlled trial. *Eur. J. Heart Fail.* **19**, 69–77 (2017).
22. Margulies, K. B. et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* **316**, 500–508 (2016).
23. Hamad, F. et al. Systematic review of glucagon-like peptide one receptor agonist liraglutide of subjects with heart failure with reduced left ventricular ejection fraction. *Curr. Diabetes Rev.* **17**, 280–292 (2021).
24. Lingvay, I. et al. Semaglutide for cardiovascular event reduction in people with overweight or obesity: SELECT study baseline characteristics. *Obesity* **31**, 111–122 (2023).
25. Novo Nordisk A/S. Semaglutide 2.4 mg reduces the risk of major adverse cardiovascular events by 20% in adults with overweight or obesity in the SELECT trial. Press release 8 August 2023. https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=166301 (2023).
26. Lincoff, A. M. et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N. Engl. J. Med.* **389**, 2221–2232 (2023).
27. Ledwidge, M. et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* **310**, 66–74 (2013).
28. Pop-Busui, R. et al. Heart failure: an underappreciated complication of diabetes. a consensus report of the american diabetes association. *Diabetes Care* **45**, 1670–1690 (2022).
29. Pfeffer, M. A. et al. Angiotensin receptor-neprilysin inhibition in acute myocardial infarction. *N. Engl. J. Med.* **385**, 1845–1855 (2021).
30. Solomon, S. D. et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N. Engl. J. Med.* **387**, 1089–1098 (2022).
31. Anker, S. D. et al. Empagliflozin in heart failure with a preserved ejection fraction. *N. Engl. J. Med.* **385**, 1451–1461 (2021).
32. Udell, J. A. et al. Sodium glucose cotransporter-2 inhibition for acute myocardial infarction: JACC review topic of the week. *J. Am. Coll. Cardiol.* **79**, 2058–2068 (2022).
33. Bozkurt, B. Pre-heart failure: an important opportunity to prevent a deadly disease. *JACC Heart Fail.* **11**, 1027–1031 (2023).
34. Perkovic, V. et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N. Engl. J. Med.* **380**, 2295–2306 (2019).
35. Wanner, C. et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N. Engl. J. Med.* **375**, 323–334 (2016).
36. Heerspink, H. J. L. et al. Dapagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **383**, 1436–1446 (2020).
37. Marx, N. et al. 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur. Heart J.* **44**, 4043–4140 (2023).
38. Brenner, B. M. et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N. Engl. J. Med.* **345**, 861–869 (2001).
39. Lewis, E. J. et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N. Engl. J. Med.* **345**, 851–860 (2001).
40. Filippatos, G. et al. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. *Circulation* **145**, 437–447 (2022).
41. Filippatos, G. et al. Finerenone and heart failure outcomes by kidney function/albuminuria in chronic kidney disease and diabetes. *JACC Heart Fail.* **10**, 860–870 (2022).
42. McDonagh, T. A. et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **44**, 3627–3639 (2023).
43. McMurray, J. J. et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N. Engl. J. Med.* **371**, 993–1004 (2014).
44. McMurray, J. J. V. et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* **381**, 1995–2008 (2019).
45. Packer, M. et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N. Engl. J. Med.* **383**, 1413–1424 (2020).
46. Damman, K. et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail.* **6**, 489–498 (2018).
47. Chandra, A. et al. Effects of sacubitril/valsartan on physical and social activity limitations in patients with heart failure: a secondary analysis of the PARADIGM-HF trial. *JAMA Cardiol.* **3**, 498–505 (2018).
48. Khariton, Y. et al. Association between sacubitril/valsartan initiation and health status outcomes in heart failure with reduced ejection fraction. *JACC Heart Fail.* **7**, 933–941 (2019).
49. Kosiborod, M. N. et al. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. *Circulation* **141**, 90–99 (2020).
50. Doughty, R. N. et al. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo substudy. *Circulation* **109**, 201–206 (2004).
51. Bozkurt, B. et al. New insights into mechanisms of action of carvedilol treatment in chronic heart failure patients—a matter of time for contractility. *J. Card. Fail.* **18**, 183–193 (2012).
52. Poole-Wilson, P. A. et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* **362**, 7–13 (2003).
53. No authors listed.Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* **353**, 2001–2007 (1999).
54. Konstam, M. A. et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. *Circulation* **86**, 431–438 (1992).
55. Cicoira, M. et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J. Am. Coll. Cardiol.* **40**, 304–310 (2002).
56. Januzzi, J. L. Jr et al. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA* **322**, 1085–1095 (2019).
57. Khan, M. S. et al. Reverse cardiac remodeling following initiation of sacubitril/valsartan in patients with heart failure with and without diabetes. *JACC Heart Fail.* **9**, 137–145 (2021).
58. Lee, M. M. Y. et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation* **143**, 516–525 (2021).
59. Santos-Gallego, C. G. et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. *J. Am. Coll. Cardiol.* **77**, 243–255 (2021).
60. Tromp, J. et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC Heart Fail.* **10**, 73–84 (2022).
61. Wachter, R. et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur. J. Heart Fail.* **21**, 998–1007 (2019).
62. Velazquez, E. J. et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N. Engl. J. Med.* **380**, 539–548 (2019).
63. Desai, A. S. et al. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* **322**, 1077–1084 (2019).
64. Bohm, M. et al. Empagliflozin improves cardiovascular and renal outcomes in heart failure irrespective of systolic blood pressure. *J. Am. Coll. Cardiol.* **78**, 1337–1348 (2021).
65. McMurray, J. J. V. et al. Effects of dapagliflozin in patients with kidney disease, with and without heart failure. *JACC Heart Fail.* **9**, 807–820 (2021).

66. Ferreira, J. P. et al. Interplay of mineralocorticoid receptor antagonists and empagliflozin in heart failure: EMPEROR-reduced. *J. Am. Coll. Cardiol.* **77**, 1397–1407 (2021).
67. Bozkurt, B. et al. Neprilysin inhibitors in heart failure. *JACC Basic Transl. Sci.* **8**, 88–105 (2022).
68. Mann, D. L. et al. Effect of treatment with sacubitril/valsartan in patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA Cardiol.* **7**, 17–25 (2022).
69. Vaduganathan, M. et al. Time to clinical benefit of dapagliflozin in patients with heart failure with mildly reduced or preserved ejection fraction: a prespecified secondary analysis of the DELIVER randomized clinical trial. *JAMA Cardiol.* **7**, 1259–1263 (2022).
70. Bozkurt, B. How to initiate and uptitrate GDMT in heart failure: practical stepwise approach to optimization of GDMT. *JACC Heart Fail.* **10**, 992–995 (2022).
71. Mebazaa, A. et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet* **400**, 1938–1952 (2022).
72. Voors, A. A. et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat. Med.* **28**, 568–574 (2022).
73. Bhatt, D. L. et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N. Engl. J. Med.* **384**, 117–128 (2021).
74. Bozkurt, B. What to and not to monitor for uptitration of GDMT in patients with heart failure: the case for patient self-uptitration of GDMT. *JACC Heart Fail.* **10**, 881–884 (2022).
75. Bhatt, A. S., DeVore, A. D., DeWald, T. A., Swedberg, K. & Mentz, R. J. Achieving a maximally tolerated beta-blocker dose in heart failure patients: is there room for improvement? *J. Am. Coll. Cardiol.* **69**, 2542–2550 (2017).
76. Packer, M. et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* **100**, 2312–2318 (1999).
77. Mohebi, R. et al. Dose-response to sacubitril/valsartan in patients with heart failure and reduced ejection fraction. *J. Am. Coll. Cardiol.* **80**, 1529–1541 (2022).
78. Rohde, L. E. et al. Sacubitril/valsartan and sudden cardiac death according to implantable cardioverter-defibrillator use and heart failure cause: a PARADIGM-HF analysis. *JACC Heart Fail.* **8**, 844–855 (2020).
79. Taylor, A. L. et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N. Engl. J. Med.* **351**, 2049–2057 (2004).
80. Armstrong, P. W. et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* **382**, 1883–1893 (2020).
81. Anker, S. D. et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N. Engl. J. Med.* **361**, 2436–2448 (2009).
82. Ponikowski, P. et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur. Heart J.* **36**, 657–668 (2015).
83. Ponikowski, P. et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* **396**, 1895–1904 (2020).
84. Mentz, R. J. et al. Ferric carboxymaltose in heart failure with iron deficiency. *N. Engl. J. Med.* **389**, 975–986 (2023).
85. Ponikowski, P. et al. Efficacy of ferric carboxymaltose in heart failure with iron deficiency: an individual patient data meta-analysis. *Eur. Heart J.* **44**, 5077–5091 (2023).
86. Salah, H. M., Fudim, M. & Burkhoff, D. Device interventions for heart failure. *JACC Heart Fail.* **11**, 1039–1054 (2023).
87. Hahn, R. T., Brener, M. I., Cox, Z. L., Pinney, S. & Lindenfeld, J. Tricuspid regurgitation management for heart failure. *JACC Heart Fail.* **11**, 1084–1102 (2023).
88. Okumus, N., Abraham, S., Puri, R. & Tang, W. H. W. Aortic valve disease, transcatheter aortic valve replacement, and the heart failure patient: a state-of-the-art review. *JACC Heart Fail.* **11**, 1070–1083 (2023).
89. Lander, M. M. et al. Mitral interventions in heart failure. *JACC Heart Fail.* **11**, 1055–1069 (2023).
90. Bozkurt, B. et al. Cardiac rehabilitation for patients with heart failure: JACC expert panel. *J. Am. Coll. Cardiol.* **77**, 1454–1469 (2021).
91. Abraham, W. T. et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. *Eur. Heart J.* **42**, 700–710 (2021).
92. Greene, S. J. et al. Worsening heart failure: nomenclature, epidemiology, and future directions: JACC review topic of the week. *J. Am. Coll. Cardiol.* **81**, 413–424 (2023).
93. Bozkurt, B. Nonresponse to heart failure therapy: an important trajectory. *JACC Heart Fail.* **11**, 729–732 (2023).
94. Morris, A. A. et al. Guidance for timely and appropriate referral of patients with advanced heart failure: a scientific statement from the American Heart Association. *Circulation* **144**, e238–e250 (2021).
95. Bozkurt, B. Treatment of advanced (stage D) heart failure in the new era. *JACC Heart Fail.* **11**, 258–260 (2023).
96. Solomon, S. D. et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N. Engl. J. Med.* **381**, 1609–1620 (2019).
97. Pitt, B. et al. Spironolactone for heart failure with preserved ejection fraction. *N. Engl. J. Med.* **370**, 1383–1392 (2014).
98. Yusuf, S. et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* **362**, 777–781 (2003).
99. Solomon, S. D. et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur. Heart J.* **37**, 455–462 (2016).
100. Lund, L. H. et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur. J. Heart Fail.* **20**, 1230–1239 (2018).
101. Solomon, S. D. et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation* **141**, 352–361 (2020).
102. Cleland, J. G. F. et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur. Heart J.* **39**, 26–35 (2018).
103. Desai, A. S., Lam, C. S. P., McMurray, J. J. V. & Redfield, M. M. How to manage heart failure with preserved ejection fraction: practical guidance for clinicians. *JACC Heart Fail.* **11**, 619–636 (2023).
104. Halliday, B. P. et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* **393**, 61–73 (2019).
105. Kitzman, D. W. et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* **315**, 36–46 (2016).
106. Shimada, Y. J., Tsugawa, Y., Brown, D. F. M. & Hasegawa, K. Bariatric surgery and emergency department visits and hospitalizations for heart failure exacerbation: population-based, self-controlled series. *J. Am. Coll. Cardiol.* **67**, 895–903 (2016).
107. Doumouras, A. G. et al. Bariatric surgery and cardiovascular outcomes in patients with obesity and cardiovascular disease:: a population-based retrospective cohort study. *Circulation* **143**, 1468–1480 (2021).
108. Kosiborod, M. N. et al. Design and baseline characteristics of STEP-HFpEF program evaluating semaglutide in patients with obesity HFpEF phenotype. *JACC Heart Fail.* **11**, 1000–1010 (2023).
109. Kosiborod, M. N. et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* **389**, 1069–1084 (2023).
110. Metra, M. et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ. Heart Fail.* **5**, 54–62 (2012).
111. Logeart, D. et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J. Am. Coll. Cardiol.* **43**, 635–641 (2004).
112. Mullens, W. et al. Acetazolamide in acute decompensated heart failure with volume overload. *N. Engl. J. Med.* **387**, 1185–1195 (2022).
113. Kittleson, M. M. et al. ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. *J. Am. Coll. Cardiol.* **81**, 1076–1126 (2023).
114. Maurer, M. S. et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N. Engl. J. Med.* **379**, 1007–1016 (2018).
115. Khan, M. S. et al. Albuminuria and heart failure: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **81**, 270–282 (2023).
116. Kontorovich, A. R. Approaches to genetic screening in cardiomyopathies: practical guidance for clinicians. *JACC Heart Fail.* **11**, 133–142 (2023).

Competing interests

B.B. has served in consultation or advisory committee roles for Abiomed, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Daiichi Sankyo, Johnson & Johnson, Hanger Institute, Merck, Occlutech, Regeneron, Roche, Sanofi, scPharmaceuticals, Vifor and Zoll/Respicardia, and is on the clinical event committees of Abbott Vascular and the data safety monitoring committees of Cardurion, Liva Nova, Novo Nordisk and Renovacor.

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